

Laboratory Data Management AND Reporting

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INTRODUCTION:

Clinical studies are a logistical nightmare with varied requirements for investigators and clinical monitors. These studies are complicated and that by definition means expensive and time consuming. More than one source has estimated that new chemical entities require approximately at least \$10MM and 10 years for new drug application completion. Anything that reduces strains on any of these resources is worth investigating.

There are important safety considerations to the participants in studies. A recent Phase III project was terminated prematurely because there were five deaths during the study. These deaths were ultimately classified as drug-related. The reason for the language used is that as the deaths were occurring, there was no immediate connection between the study sites and the deaths. The deaths were occurring in geographically separated centers in a multi-center study. Evidence for all of this is located in the Federal Register, in the preamble to rule-making by the Food & Drug Administration (FDA) (Federal Register 59:207 pp54046-54064, Oct 27, 1994 -- [Slide 1]).

This case, while unfortunate, was preventable. Liver and pancreatic laboratory values were elevated during the course of the study. The problem was, no one made the connection that this was happening! Typically, laboratory data gets reviewed last in the clinical study data stream, despite laboratory data being usually available during the course of the study.

One of the difficulties with laboratory data is it has insomnia-eliminating properties. A strong will and lots of coffee are required to review laboratory data. This is an unfortunate circumstance. One of the advantages that computers offer, coupling SAS to do this 'scut' work is an appropriate technology step.

MATERIALS AND METHODS:

The FDA has a flexible attitude toward the presentation of laboratory data. The FDA attitude is one of welcoming all approaches. These attributes facilitate everyone's objectives:

1. Computer process the data -- let pc's do the work.
2. Present the data such that everyone can easily comprehend the results.
3. Fully and completely identify the output to facilitate use of the output and tables.
4. Accommodate those at the working level whether in laboratories, clinics or offices.
Make the tabular output easier to follow from lab test to lab test.
5. Ensure the presentation complies with FDA's guidelines, but that all potential users, be they clinicians, data processors, medical writers and regulatory types can understand and see any action that may be required.
 - > Data processors must validate the results to themselves and clinicians.
 - > Statisticians must verify the relevance of the result.
 - > Clinical types have to take the lab results back to an investigator and explain the tables.
 - > Regulatory types may have to prepare an Adverse Drug Reaction report for FDA!

This is no place for statistical testing with gay abandon. Tests conducted must be appropriate and defensible. If there are 'outliers' these 'outliers' must be identified -- are they real or are they flukes? Any one dealing with these issues wants to know there is a reasoned decision-support system in place.

The FDA has two criteria that must be observed if you read and follow the 'gospel' according to FDA (Guideline for The Format and Content of the Clinical and Statistical Sections of New Drug Applications -- [Slide 2] [pages 76 & 77ff provide detailed guidance on laboratory data presentation.]) (1) By-Patient listings are required for physicians and medical reviewers, and (2) By-Test listings are required for data analysis. FDA is very clear about wanting demographic information (age, race and sex -- minimum) along with the normal ranges for the laboratories

involved. The demographic data and normal range information are appropriate for the By-Patient listings. The normal ranges are also of particular interest in the By-Test listings.

RESULTS:

The By-Patient Listing is almost a 'no-brainer'. The objective here is to put as much information on a page as possible. A number of features within SAS support this. Notice please there is demography that relates to the patient. The laboratory tests are grouped. There is the 'by visit' orientation that FDA seeks; where each row represents a visit. (Slide 3. A,...D)

The By-Test Listing is the challenge. This is the place for creativity. A semigraphical approach lends itself to this presentation best: Plots are easily understood and intuitive.

A moment of studying the output here will be useful. Please examine:

- A unique table number to this plot, which identifies the table and test.
- The normal ranges with units are provided for the gender/race/age groups - though most adults groups are about equivalent. We'll see male and female plots later.
- SAS plots by density, A=1, B=2, ...
- Notice also the HREF's for the normal ranges in the titles.
- This plot gets dense and difficult to precisely interpret. (Slide 4)

An option exists: A plot of the means 'over time' for each treatment group. In cholesterol lowering drug, this plot has some information of interest. Notice the location of TESTDRUG 'T' across the page. (Slide 5)

Recall the normal range from the plot. One of the pieces that FDA is firm about is wanting to know which values are out of (normal) range. There are two sets of ranges the normal ranges indicated by these slides: (Slide 6)

- The 'normal range' of cholesterol for adults (90-199 mg/dl) yields 'abnormals'.
- The 'extreme range' extends the 'normal range' (45-298.5 mg/dl) yields 'extremes'.

This features identification of 'Abnormals' which are outside the normal range, but within the 'extreme range'. NOBODY wants to review normal values! Which is the reason for this exception report -- OUTLIERS ONLY! It lists cholesterol results that are above or below the normal range, but not outside Lomin or Himax. (Slide 7)

- Identification of the patient, age, race, sex, draw date and results.
- Counter at the bottom of the treatment group set.
- If no 'Abnormals' this listing is not produced.

This identifies 'Extremes', those outside Lomin or Himax; exceptions only, no normals to be reviewed again. Similar to previous slide. (Slide 8).

- Identification of the patient...
- Counter at the bottom of the treatment group set.
- If no 'Extremes' this listing is not produced.

This is an added feature! A summary of important groups: Treatments and Responses. (Slide 9)

- Familiar terms: Normals/Abnormals/Extremes - by treatment group.
- See any familiar numbers? N=264 Abnormals for Testdrug. N=3 Extremes for Placebo.
- If there are no 'Abnormals' or 'Extremes', this table will not produce.

(Slide 10) This is the second part of (Slide 9). The statistical results from the crosstabulation of TmTCod*LabRslt. ChiSquare tells the relative importance of frequencies.

This is an example of plots where the normals are based on gender. (Slide 11)

- (A) Males for creatinine kinase with the crosstabulation of results.
- (B) Females for creatinine kinase with the crosstabulation of results.

New turf! This slide makes the baseline comparison between treatments. Two parts, the ANOVA and the multiple range test (SNK). (Slide 12 A/B)

More new turf! This slide compares the treatments using covariance at Rkdate=10. (Slide 13 A/B)
Two parts, this brings the baseline from the previous slide over as the 'COVTE'. This also uses the multiple range test (SNK).

The end-of-study test of cholesterol. (Slide 14 A/B) Using the baseline as 'COVTE' again and Rkdate=20, the final observation of cholesterol in the study. Also uses the multiple range test (SNK).

TECHNICAL NOTES:

The attributes of SAS make such a system possible. Notably, the self-limiting feature is especially useful. Elements that have no requirement, are not produced throughout the system. This includes the listings of 'abnormals' and 'extremes' as well as the non-parametric test of frequencies. If the data for a table, listing or test is not present, the table, listing or test is not produced.

The choice of limits for 'abnormals' and 'extremes' is easily reset, based on medical department concurrence. Many physicians conducting clinical studies do not want to be bothered with 'abnormals' that are not 'really abnormal' therefore, the 'extremes' are the set that cause physicians to get interested.

This entire system is extremely heavily embedded with macros. There are multiple macros calling macros. The biggest difficulty with it is getting the data 'to fit'. The issues then resolve to those of calling the macros when desired results are wanted.

Bringing the baseline forward as a covariate for testing later observations in a macro environment took quite a bit of effort to get to work correctly. A large quantity of time was spent checking the results to ensure that the desired element was correctly located for subsequent testing.

A note to those conducting statistical testing: The analysis of variance and covariance are applied here and throughout on continuous variables. Most laboratory tests satisfy these criteria. A few may not, there is a non-parametric test regarding the Normals, Abnormals and Extremes.

CONCLUSION:

Notice in these last few slides there have been the most desired result for a cholesterol lowering drug: No difference at baseline, with statistically different covariance results favoring the Testdrug! Not only did we get the most desirable results, we have an effect method of reporting and presentation.

This system has many strengths and attributes:

1. Computer-processes laboratory data.
2. Presents laboratory data in an intuitive, plot-oriented format.
3. Presentations are fully and uniquely identified for those at the working level -- be they Clinical Research Assistant's, Clinical Data Assistant's, Medical Writers or Regulatory Reviewers. The 'Abnormal' or 'Extreme' listings for every test can be easily 'run' and carried back to an investigational site for discussion with an investigator or verification against a case record form. The full set of features does not have to always be 'run'. This makes monitoring laboratory data from clinical studies possible and easier.
4. The CRA's, CDA's, writers, regulatory reviewers may want only segments for meetings or discussions -- these can be delivered. Additionally, the identification features make dealing with the output infinitely easier for those responsible for closing a large clinical study and writing a drug application. Also, SAS System's self-limiting nature does not produce unnecessary tables or listings.
5. The major advantage, when all options are used, this system fully complies with FDA guidelines.
6. A final attribute: While the data presented here was laboratory data from a human study, this system easily applies to animal studies. Because the nature of this data is continuous, this will apply to monitoring other continuous data: heart rate, blood pressures, respiration rates and weights.

Registered

Thursday
October 27, 1994

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 20, et al.
Adverse Experience Reporting
Requirements for Human Drug and
Licensed Biological Products; Proposed
Rule



GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

TITLE1 SPONSOR'S NAME ----- 22:12 Monday, August 17, 1998
 TITLE2 Protocol title -----
 TITLE3 Protocol title -----
 TITLE4 Protocol title -----
 TITLE5 Protocol number -----

APPENDIX C-1(A): Individual details (lipids)

----- Pt No=3x Pt Inits=XYZ Age=6y Race=Whi Sex=Mal Treat=PLACEBO -----

Spec Date	Chol	Trig	HDL	LDL	VLDL	Chol/HDL Ratio
05/11/92						
09/17/92	171	147	40	102	29	4.3
11/06/92	155	146	41	85	29	3.8
02/22/93						
04/05/93	166	185	38	91	37	4.4
05/06/93	154	126	31	98	25	5.0
06/09/93	151	131	33	92	26	4.6
07/13/93	167	107	35	111	21	4.8
08/16/93	177	127	39	113	25	4.5
09/16/93	172	119	39	109	24	4.4
10/19/93	175	82	48	111	16	3.6
12/21/93	151	92	42	91	18	3.6
03/03/94	158	101	44	94	20	3.6
05/05/94	151	66	52	86	13	2.9
07/07/94	164	62	43	109	12	3.8
09/06/94	151	36	57	87	7	2.6
11/08/94	167	73	47	105	15	3.6
01/05/95	186	92	47	121	18	4.0
02/28/95	158	77	42	101	15	3.8
04/13/95	185	62	52	121	12	3.6
04/13/95	185	62	52	121	12	3.6
04/13/95	185	62	52	121	12	3.6
06/08/95	168	83	46	105	17	3.7
08/08/95	183	81	48	119	16	3.8
10/05/95	164	110	37	105	22	4.4

TITLE1 SPONSOR'S NAME ----- 22:12 Monday, August 17, 1998
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APPENDIX C-1(B): Individual details (chemistry)

----- Pt No=3x Pt Inits=XYZ Age=6y Race=Whi Sex=Mal Treat=PLACEBO -----

SPDATE	BUN	CREAT	TPROT	ALB	TBILI	NA	K	CHLO	GLUC	CA	P	FBRGN	INS	ALT	AST	LDH	ALKPHS	URACD	CK
05/11/92		1.2							93	8.9	2.6					137			38
09/17/92	14	1.2	7.0	3.8	0.5	143	4.7	106	94	9.4	2.8					143	80	6.0	
11/06/92																			
02/22/93												247	6.5						
04/05/93									82								82		
05/06/93									104							127	106		56
06/09/93									96							128	101		57
07/13/93									78							141	98		96
08/16/93									84							153	109		64
09/16/93									91							154	101		82
10/19/93	13	1.1	8.0	4.2	0.6	140	4.1	103	78	9.3	2.9					163	115	6.9	85
12/21/93									102							203	107		66
03/03/94									93							146	137		69
05/05/94	15	1.2	8.1	4.1	0.6	143	4.2	103	87	9.3	3.1	465	5.4			163	130	7.3	69
07/07/94									42							160	137		62
09/06/94									71							193	116		204
11/08/94	14	1.3	8.3	4.3	0.6	142	4.4	103	88	9.6	3.6	450	5.0			177	117	8.2	73
01/05/95									92							171	104		72
02/28/95									81							185	105		95
04/13/95	13	1.1	8.2	4.4	0.5	141	4.0	104	87	9.3	3.2	397	9.3			17.2	121	7.2	178
04/13/95	13	1.1	8.2	4.4	0.5	141	4.0	104	87	9.3	3.2	397	9.3			40	121	7.2	178
04/13/95	13	1.1	8.2	4.4	0.5	141	4.0	104	87	9.3	3.2	397	9.3			233	121	7.2	178
06/08/95									86							193	112		60
08/08/95									84							270	108		87
10/05/95	15	1.3	8.3	4.5	0.6	141	3.9	103	86	9.2	2.8	361	8.5			187	135	8.2	62

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APPENDIX C-1(C): Individual details (hematology & differential pcts)

----- Pt No=3x Pt Initls=XYZ Age=6y Race=Whi Sex=Mal Treat=PLACEBO -----

Spec Date	RBC	Hgb	Hct	WBC	Plat Cnt	Baso Pct	Eos Pct	Lymp Pct	Mono Pct	Neut Pct
05/11/92										
09/17/92	4.69	14.3	42.1	6.2	202.0	0.8	3.9	34.2	10.4	50.7
11/06/92										
02/22/93										
04/05/93										
05/06/93										
06/09/93										
07/13/93										
08/16/93										
09/16/93										
10/19/93	4.74	14.7	42.8	6.5	204.0	0.4	3.0	34.8	9.7	52.1
12/21/93										
03/03/94										
05/05/94	4.50	14.3	41.8	5.1	209.0	0.6	2.9	36.5	10.4	49.6
07/07/94										
09/06/94										
11/08/94	4.53	14.4	42.1	5.6	247.0	0.5	3.0	34.5	9.7	52.3
01/05/95										
02/28/95										
04/13/95	4.73	14.8	43.5	9.7	199.0	0.3	2.1	15.8	7.1	74.7
04/13/95	4.73	14.8	43.5	9.7	199.0	0.3	2.1	15.8	7.1	74.7
04/13/95	4.73	14.8	43.5	9.7	199.0	0.3	2.1	15.8	7.1	74.7
06/08/95										
08/08/95										
10/05/95	4.42	14.6	41.4	5.1	193.0	0.4	5.0	38.3	8.9	47.4

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APPENDIX C-1(D): Individual details (differential counts)

----- Pt No=3x Pt Inits=XYZ Age=6y Race=Whi Sex=Mal Treat=PLACEBO -----

Spec Date	Baso Cnt	Eos Cnt	Lymp Cnt	Mono Cnt	Neut Cnt	Leuk Cnt	Poly Cnt	Band Cnt	Segs Cnt
05/11/92									
09/17/92	0.00	0.20	2.1	0.60	3.30				
11/06/92									
02/22/93									
04/05/93									
05/06/93									
06/09/93									
07/13/93									
08/16/93									
09/16/93									
10/19/93	0.00	0.20	2.3	0.60	3.40				
12/21/93									
03/03/94									
05/05/94	0.00	0.10	1.9	0.50	2.60				
07/07/94									
09/06/94									
11/08/94	0.00	0.20	1.9	0.50	3.00				
01/05/95									
02/28/95									
04/13/95	0.00	0.20	1.5	0.70	7.30				
04/13/95	0.00	0.20	1.5	0.70	7.30				
04/13/95	0.00	0.20	1.5	0.70	7.30				
06/08/95									
08/08/95									
10/05/95	0.00	0.30	2.0	0.50	2.30				

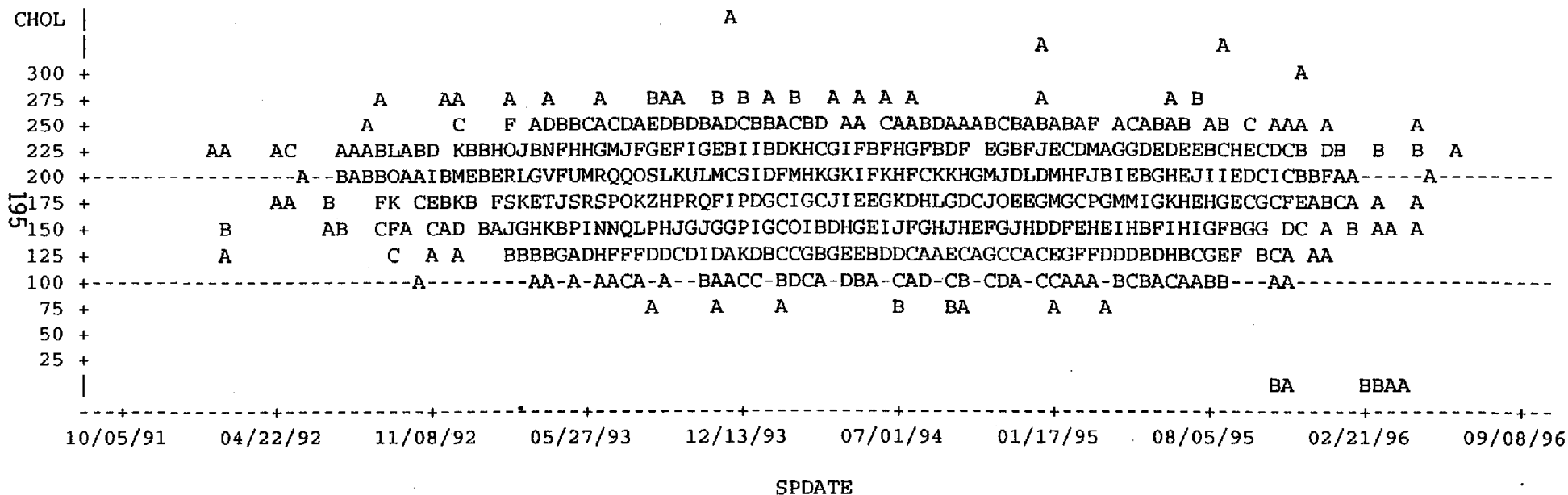
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TITLE2 Protocol title -----
TITLE3 Protocol title -----
TITLE4 Protocol title -----
TITLE5 Protocol number -----

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FIGURE C-2A: Cholesterol
(Sex=E, Normal Range: 90-199 mg/dl)

Plot of CHOL*SPDATE. Legend: A = 1 obs, B = 2 obs, etc.

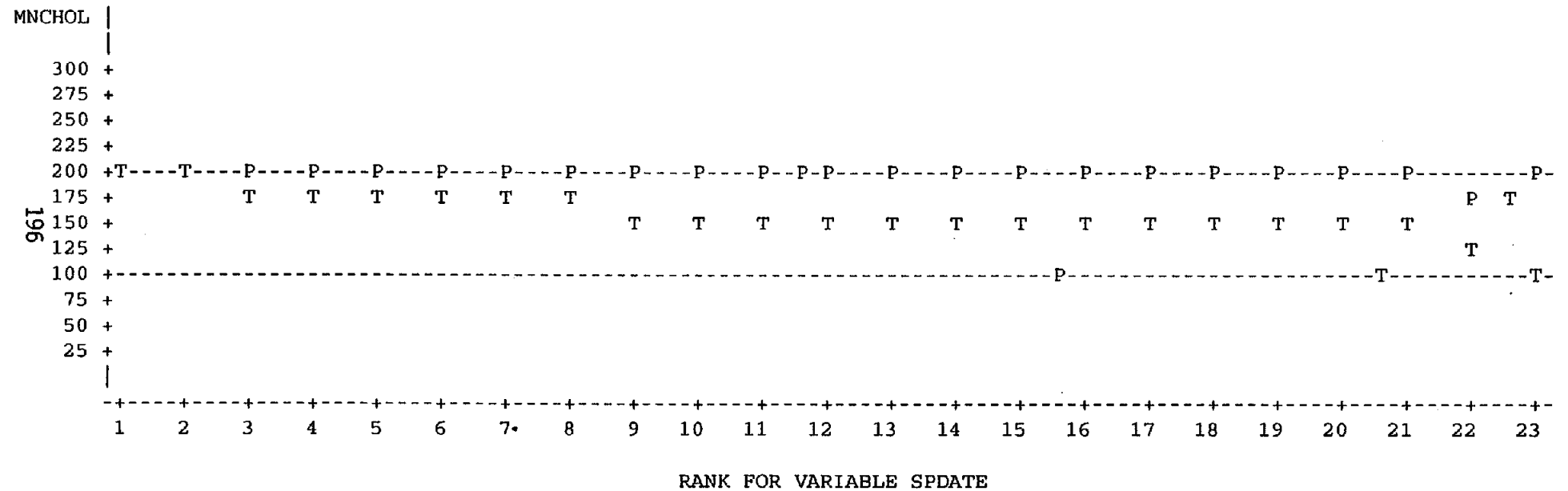


NOTE: 4 obs hidden.

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Test plot of means by tmt by rankdates

Plot of MNCHOL*RKDATE. Symbol is value of RXCODE.



NOTE: 2 obs hidden.

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FIGURE C-2A: Abnormal Cholesterol, equal or within +/-50% NR
 (Sex=E, Normal Range: 90-199 mg/dl)

----- Treatment=TESTDRUG -----

PAT	INI	DMAGE	DMRACE	DMSEX	SPDATE	LOMIN	HIMAX	CHOL
1	ABC	51	Whi	Mal	05/07/92	45	298.5	234
1	ABC	51	Whi	Mal	09/15/92	45	298.5	212
1	ABC	51	Whi	Mal	02/01/93	45	298.5	206
3	DEF	42	Whi	Mal	09/17/92	45	298.5	215
3	DEF	42	Whi	Mal	12/30/92	45	298.5	202
3	DEF	42	Whi	Mal	02/01/93	45	298.5	209
5	GHI	55	His	Mal	09/18/92	45	298.5	218
5	GHI	55	His	Mal	12/09/92	45	298.5	226
5	GHI	55	His	Mal	02/02/93	45	298.5	202
5	GHI	55	His	Mal	03/02/93	45	298.5	207
9	JKL	64	Whi	Mal	02/03/93	45	298.5	233
9	JKL	64	Whi	Mal	05/04/93	45	298.5	206
9	JKL	64	Whi	Mal	02/09/95	45	298.5	206
10	MNO	62	Whi	Mal	02/08/93	45	298.5	211
11	PQR	63	Whi	Mal	09/17/92	45	298.5	221
11	PQR	63	Whi	Mal	11/05/92	45	298.5	219
11	PQR	63	Whi	Mal	03/09/93	45	298.5	200
11	PQR	63	Whi	Mal	04/07/93	45	298.5	208
17	STU	61	Whi	Mal	09/15/92	45	298.5	215
17	STU	61	Whi	Mal	12/14/92	45	298.5	230
17	STU	61	Whi	Mal	02/10/93	45	298.5	238
17	STU	61	Whi	Mal	03/09/93	45	298.5	204
17	STU	61	Whi	Mal	05/03/94	45	298.5	215
17	STU	61	Whi	Mal	11/08/94	45	298.5	212

N = 264

TITLE1 SPONSOR'S NAME :-----
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FIGURE C-2A: Extreme Cholesterol, outside +/-50% NR
 (Sex=E, Normal Range: 90-199 mg/dl)

----- Treatment=PLACEBO -----

PAT	INI	DMAGE	DMRACE	DMSEX	SPDATE	LOMIN	HIMAX	CHOL
18	ZYX	52	Whi	Mal	01/05/95	45	298.5	326
236	WVU	70	Whi	Mal	08/17/95	45	298.5	335
604	TSR	69	Whi	Fem	11/18/93	45	298.5	362

N = 3

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FIGURE C-2A: Nonparametric test of Cholesterol
 (Sex=E, Normal Range: 90-199 mg/dl)
 (Normal w/i NR, Abnormls w/i Lomin/Himax, Extremes > Lomin/Himax)
 (Lomin = NR Min * 0.5, Himax = NR Max * 1.50)

TABLE OF RXCODE BY LABRSLT

RXCODE(Treatment) LABRSLT(Laboratory Results)

Frequency				
Percent	Normals	Abnormls	Extremes	Total
-----+-----+-----+-----+				
TESTDRUG	1155	264	0	1419
	41.37	9.46	0.00	50.82
-----+-----+-----+-----+				
PLACEBO	714	656	3	1373
	25.57	23.50	0.11	49.18
-----+-----+-----+-----+				
Total	1869	920	3	2792
	66.94	32.95	0.11	100.00

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FIGURE C-2A: Nonparametric test of Cholesterol
 (Sex=E, Normal Range: 90-199 mg/dl)
 (Normal w/i NR, Abnormls w/i Lomin/Himax, Extremes > Lomin/Himax)
 (Lomin = NR Min * 0.5, Himax = NR Max * 1.50)

STATISTICS FOR TABLE OF RXCODE BY LABRSLT

Statistic	DF	Value	Prob
Chi-Square	2	273.399	0.001
Likelihood Ratio Chi-Square	2	280.932	0.001
Mantel-Haenszel Chi-Square	1	273.278	0.001
Phi Coefficient		0.313	
Contingency Coefficient		0.299	
Cramer's V		0.313	

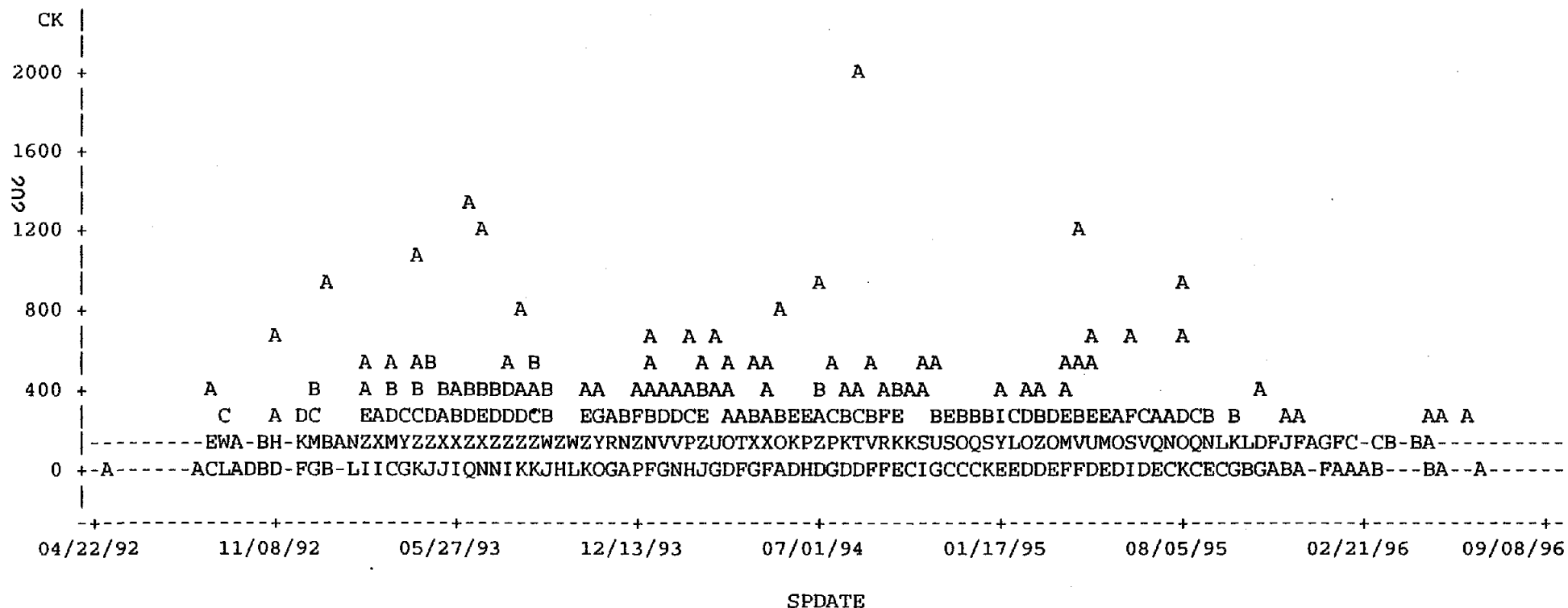
Sample Size = 2792

WARNING: 33% of the cells have expected counts less
 than 5. Chi-Square may not be a valid test.

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FIGURE C-3S: Creatinine Kinase
 (Sex=M, Normal Range: 24-195 IU/L)

Plot of CK*SPDATE. Legend: A = 1 obs, B = 2 obs, etc.



NOTE: 98 obs hidden.

TITLE1 SPONSOR'S NAME ----- 23:07 Monday, August 17, 1998
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FIGURE C-3S: Nonparametric test of Creatinine Kinase
 (Sex=M, Normal Range: 24-195 IU/L)
 (Normal w/i NR, Abnormls w/i Lomin/Himax, Extremes > Lomin/Himax)
 (Lomin = NR Min * 0.5, Himax = NR Max * 1.50)

TABLE OF RXCODE BY LABRSLT

RXCODE(Treatment)		LABRSLT(Laboratory Results)			
Frequency					
Percent	Normals	Abnormls	Extremes	Total	
-----+					
TESTDRUG	1079	94	47	1220	
	44.09	3.84	1.92	49.86	
-----+					
PLACEBO	1051	102	74	1227	
	42.95	4.17	3.02	50.14	
-----+					
Total	2130	196	121	2447	
	87.05	8.01	4.94	100.00	

FIGURE C-3S: Creatinine Kinase
(Sex=F, Normal Range: 24-170 IU/L)

[illegible]

TITLE1 SPONSOR'S NAME ----- 23:07 Monday, August 17, 1998
 TITLE2 Protocol title -----
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FIGURE C-3S: Nonparametric test of Creatinine Kinase
 (Sex=F, Normal Range: 24-170 IU/L)
 (Normal w/i NR, Abnormls w/i Lomin/Himax, Extremes > Lomin/Himax)
 (Lomin = NR Min * 0.5, Himax = NR Max * 1.50)

TABLE OF RXCODE BY LABRSLT

RXCODE (Treatment)		LABRSLT (Laboratory Results)		
Frequency	Percent	Normals	Abnormls	Extremes
Total				
TESTDRUG	117 57.92	3 1.49	1 0.50	121 59.90
PLACEBO	80 39.60	0 0.00	1 0.50	81 40.10
Total	197 97.52	3 1.49	2 0.99	202 100.00

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Test at baseline for Chol (rkdate=1)

General Linear Models Procedure

Dependent Variable: CHOL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	212.27558494	212.27558494	0.24	0.6224
Error	141	122852.56357590	871.29477713		
Corrected Total	142	123064.83916084			

206	R-Square	C.V.	Root MSE	CHOL Mean
	0.001725	15.47242	29.51770278	190.77622378

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RXCODE	1	212.27558494	212.27558494	0.24	0.6224

Source	DF	Type IV SS	Mean Square	F Value	Pr > F
RXCODE	1	212.27558494	212.27558494	0.24	0.6224

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Test at baseline for Chol (rkdate=1)

General Linear Models Procedure

Student-Newman-Keuls test for variable: CHOL

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 871.2948

WARNING: Cell sizes are not equal.

Harmonic Mean of cell sizes= 71.4965

Number of Means 2

Critical Range 9.7599331

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	RXCODE
A	191.986	72	PLACEBO
A	189.549	71	TESTDRUG

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Test at midstudy for Chol (rkdate=10)

General Linear Models Procedure

Dependent Variable: CHOL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	118445.83183612	59222.91591806	102.18	0.0001
Error	136	78827.70773223	579.61549803		
Corrected Total	138	197273.53956835			

	R-Square	C.V.	Root MSE	CHOL Mean
	0.600414	13.45416	24.07520505	178.94244604

Source	DF	Type III SS	Mean Square	F Value	Pr > F
COVTE	1	42361.82435887	42361.82435887	73.09	0.0001
RXCODE	1	73371.24020843	73371.24020843	126.59	0.0001

Source	DF	Type IV SS	Mean Square	F Value	Pr > F
COVTE	1	42361.82435887	42361.82435887	73.09	0.0001
RXCODE	1	73371.24020843	73371.24020843	126.59	0.0001

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Test at midstudy for Chol (rkdate=10)

General Linear Models Procedure

Student-Newman-Keuls test for variable: CHOL

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 136 MSE= 579.6155

WARNING: Cell sizes are not equal.

Harmonic Mean of cell sizes= 69.4964

Number of Means 2

Critical Range 8.076696

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	RXCODE
A	202.507	69	PLACEBO
B	155.714	70	TESTDRUG

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Test at endstudy for Chol (rkdate=20)

General Linear Models Procedure

Dependent Variable: CHOL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	103250.21553269	51625.10776634	74.06	0.0001
Error	109	75975.77553874	697.02546366		
Corrected Total	111	179225.99107143			
	R-Square	C.V.	Root MSE		CHOL Mean
	0.576090	14.69725	26.40123981		179.63392857

Source	DF	Type III SS	Mean Square	F Value	Pr > F
COVTE	1	40045.56376410	40045.56376410	57.45	0.0001
RXCODE	1	58283.00097076	58283.00097076	83.62	0.0001
Source	DF	Type IV SS	Mean Square	F Value	Pr > F
COVTE	1	40045.56376410	40045.56376410	57.45	0.0001
RXCODE	1	58283.00097076	58283.00097076	83.62	0.0001

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Test at endstudy for Chol (rkdate=20)

General Linear Models Procedure

Student-Newman-Keuls test for variable: CHOL

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 109 MSE= 697.0255

WARNING: Cell sizes are not equal.

Harmonic Mean of cell sizes= 55.83929

Number of Means 2

Critical Range 9.9029816

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	RXCODE
A	204.698	53	PLACEBO
B	157.119	59	TESTDRUG